A STOCHASTIC BONE REMODELING PROCESS

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ABSTRACT

The present study describes bone remodeling simulations at a microscopic level based on a stochastic model. According to the theories of Frost [1], such a remodeling process takes place in circumscribed areas called bone multicellular units (*BMUs*). A *BMU*-level process is described taking into account the number of *BMUs* working on the trabecular bone surface, but it differs from other works [6] in that the probability of activating a *BMU* is not purely random. More precisely, locations for *BMUs* to be activated are chosen randomly on the trabecular bone surface restricted to sites expressing a local activation force up to a given threshold. Such a constraint, inspired by a model described in [12], will allow the presence of micro-cracks and damage, assumed to occur randomly, as well as the age of last bone formation to be taken into account. Implementations have been run for two dimensional simple images. Such a model will be extended to more realistic three dimensional images with the aim of calculating and validating classical $3D$ micro-architectural parameters.

Index Terms— Stochastic simulation, Germ-grain model, Cell-level process, Image processing

1. INTRODUCTION

The purpose of the current study is to propose a simulation process which mimics the trabecular bone surface remodeling. As cellular activity in bone remodeling is known to be regulated by mechanical factors and chemical factors, it is worth noting that our goal is not to simulate mechanical adaptation of bone induced by remodeling as done in [12].
The proposed simulation process is driven by a few parameters matching classical biological ones as much as possible, which make if possible to introduce realistic parameter modifications during the temporal process. Even if the remodeling process is not purely random, stochastic aspects will allow repetition of similar scenarios. Hence resulting images could be used to calculate and validate classical $3D$ micro-architectural parameters ([3], [5]) obtained from micro computed tomographic images (see figure 1). Radiographic simulated images and associated parameters could also be constructed and validated.

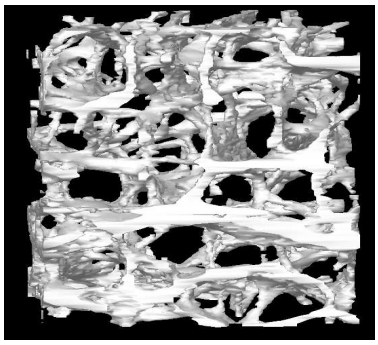

Fig. 1. A Micro Computed Tomographic $3D$ image

Let's now recall some of the main knowledge concerning the biological process. This process is a cyclical continuous one aiming at repairing damages and replacing old bone. Remodeling is mainly concerned with trabecular bone, which is a porous tissue consisting in a lattice of trabeculae (around $100m$ width) delimiting an interconnected space filled with marrow. Remodeling activity takes place in compact surface units where two main types of cells, osteoclasts and osteoblasts, have a coordinated action in what is called basic multicellular units ($BMUs$) [1]. The life cycle of a BMU consists essentially of three distinct phases illustrated by figure 2 : $Activation \rightarrow Resorption \rightarrow Formation$. Activation involves recruitment of osteoclasts precursors and their fusion into osteoclast cells. After activation, the resorption phase is carried out by these osteoclasts that attach to the surface and progress along it. The resorption phase is carried out by osteblasts which deposit osteoid and mineralize it, thus actually forming new bone. Some of the osteoblasts are encapsulated in the osteoid matrix and differentiate to bone matrix cells named osteocytes, while remaining osteoblasts continue to synthesize bone until they eventually transform to quiescent lining cells that cover the newly formed bone surface. The main two parameters that are commonly used to describe this process are activation frequency (AF), related to number of $BMUs$ activated by unit of time, and the balance be-

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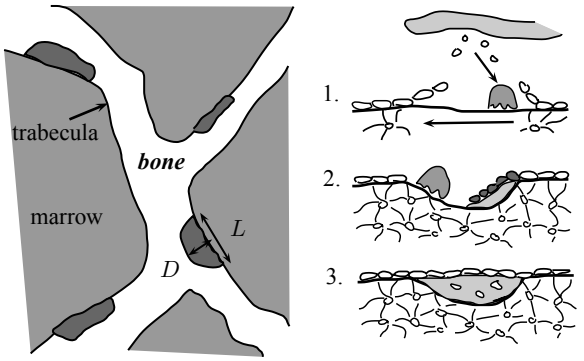


Fig. 2. Location of $BMUs$ on the trabecular bone surface and the remodeling cycle where the three phases: Activation(1), Resorption(2) and Formation(3) are represented for a single BMU.

tween formation and resorption known as bone balance (ΔB), where a negative bone balance corresponds to bone loss as observed in osteoporosis. Number and life-span of osteoclasts and osteoblasts which describe the rate of local activity are also important but not so often mentioned. It is worth noting that the reason a particular site is chosen for a BMU origination is not yet totally clear, but osteocytes are known to be involved in such an activation. Osteocytes are cells present throughout the mineralized bone matrix. They reside in lacunae and communicate with each other and probably with other surface bone cells through a canalicular network. These cells are known to act as mechanical sensors, also probably sensitive to micro-damage and to chemical factors [13].

In the following sections, $BMUs$ are described more precisely with their main parameters and a simple stochastic germ-grain model introduced. Some constraints are then added to the temporal process aiming to take into account the mineralized bone matrix state where osteocytes are found. Finally some results are presented for 2D images.

2. A GERM-GRAIN MODEL

In trabecular bone, osteoclasts resorb saucer-shaped cavities traveling across the surface digging a trench with a depth of 40 to $60\mu m$ and covering surface areas of varying sizes from as small as $50 \times 20\mu m^2$ up to $1000 \times 1000\mu m^2$ as mentioned in [9]. Such results characterize BMU shape parameters: depth (D), length (L) and width (W) in $3D$, which can be considered as variables.

Activation frequency (AF) is often used as a measure of BMU activity in trabecular bone. However, AF expresses the rate of BMU appearance in a histological slide and not the rate of origination, which is a more physiologic indicator of remodeling activity. Two formulae have been proposed in [9] to describe relationship between AF, origination frequency (OF), total bone surface area ($|S|$) and number of $BMUs$ created per unit of surface and per unit of time (N). This formula can be expressed as following, where W is the mean width of $BMUs$, R the mean rate of progression across the surface and σ the mean lifespan of $BMUs$:

$$N = \frac{AF.|S|}{W.R} = OF.|S|.\sigma$$

Knowing the trabecular bone surface S and its volume V, each $i^{th} BMU$ can be characterized by its central location X_i on surface S and its dimensions $Z_i = (L_i, W_i, D_i)$. Hence, the set of all $BMUs$ originated at one iteration of the simulation process can be seen as a stochastic marked point process $\{X_i, Z_i\}$ driving an associated germ-grain model [2] :

$$\bigcup_i \; (X_i \oplus \varepsilon_i)$$

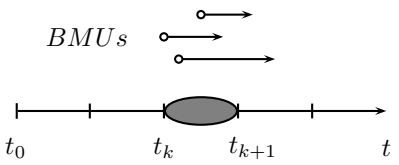
where X_i are points or germs and ε_i are surface-situated grains characterized by Z_i marks. Such germ-grain models are commonly used for describing irregular patterns observed in biology or ecology. To simulate BMU locations, a Poisson point process can be chosen as an initial approximation. Such a process is characterized by its strong independence behavior through the following two properties :

- The number of points within some finite region S is a random variable N following a Poisson distribution with mean $\lambda|S|$ for an intensity λ.
- The N points $\{X_1, \ldots, X_N\}$ are chosen independently and purely randomly located in S .

With N the number of $BMUs$ and S the set of surface pixels, intensity λ is related to the origination frequency. Dimensions characterizing BMU number i are chosen randomly as following: for convenience length is chosen as $L_i = 1 + 2(a_L + b_L.U_{i,L})$ and depth as $D_i = a_D + b_D.U_{i,D}$. Consequently, with U variables chosen as random Uniform variables onto $[0; 1]$, parameters a and b control the minimum and maximum possible values for variables L and D.

3. THE TEMPORAL PROCESS

At each k^{th} iteration of the temporal process, a number of $N(k)$ new $BMUs$ are to be generated. These $BMUs$ can be seen as those originating between t_k and t_{k+1} times as following :



BMU locations can be chosen purely randomly ($X = x$) as previously proposed with a Uniform distribution on the bone surface $\{x \in S = S(k)\}$. But there are more and more clues as to why a particular site might be chosen as a BMU origination site. The assumption that has been proposed and used in [13] is that the lack of osteocyte signals at the bone surface attracts osteoclasts for bone resorption. Such a lack can be due to mechanical disuse, to osteocyte death (apoptosis) or to fatigue micro-damage, micro-cracks for example, which occur randomly at the trabecular bone surface [14]. Consequently, locations x in the temporal process are chosen randomly, but restricted to sites expressing a local activation energy $E^a(x)$ up to a given threshold. This energy represents surface disuse and is expressed as :

$$E^a(x) = f\{\ M(y), y \in V^S(x,r)\ \}$$

where $V^S(x,r)$ denotes the bone volume in contact with the surface S in a neighborhood of the location x at maximum distance r. Moreover, $M(y)$ represents the state of the mineralized bone-matrix at site y and is related to osteocytes status. In our process $M(y)$ is simply expressed as $M(y) = a(y)$ with $a(y)$ the age from last formation, as the most plausible purpose for bone remodeling is to prevent excessive aging of bone, which can cause osteocyte death and increase susceptibility to fatigue micro-damage [3].
To control what can be seen as a targeted system [15], a threshold $Q(k)$ is calculated for each iteration of the process. An estimation of the E^a distribution onto the entire surface $S(k)$ is done and a percentile of this distribution taken as threshold $Q(k)$. Hence, in a context of a strongly targeted process, activation of a site x can be validated for example when :

$$E^a(x) > Q(k) = Q(E^a, \kappa = 85\%)$$

with $Q(k)$ estimated as : $\quad P(E^a(X) < Q(k)) = \kappa$.

Sites to be resorbed are then determined through a progression on the surface on each side of x site, randomly taking into account previously chosen length L and depth D. Note that such a process is independent of the bone-surface orientation and could be extended in a 3D version adding the random choice of a direction as in [8]. Such a surface progression is followed by a progression in depth taking into account any possible trabecular perforation which may result from this resorption process. A total of $|\varepsilon^r|$ sites having been resorbed are then subjected to be re-formed or erased during the second process. The number of sites to be re-formed is chosen as : $|\varepsilon^f| = \alpha.|\varepsilon^r|$ with $0 \leq \alpha \leq 100\%$.

4. SOME RESULTS AND PERSPECTIVES

Simulations are run with the following set of parameters related to biological ones :

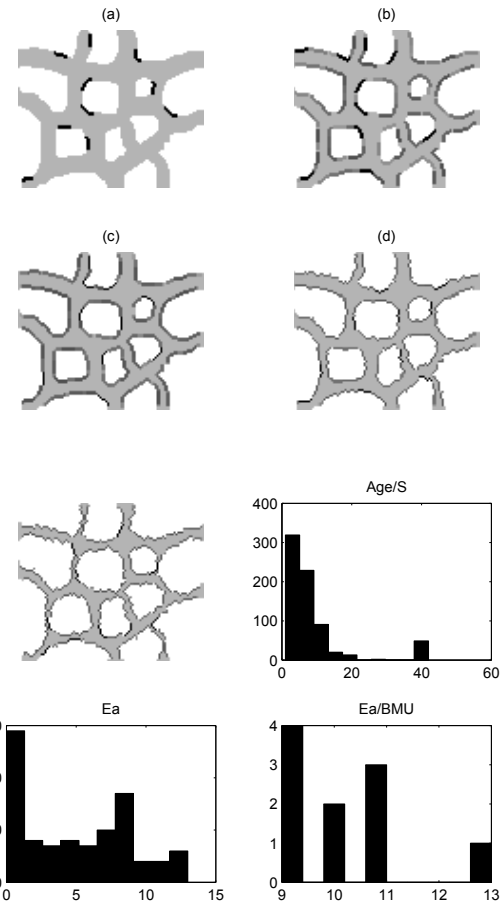


Fig. 3. A simulation with $\kappa = 85\%$. Without resorption ($\alpha = 100\%$) until the 20^{th} iteration, afterwards resorption with $\alpha = 50\%$. Histograms are associated to distributions relative to the last image. High value observation for Age on surface S (Age/S) is due to the apparition of old bone in surface as a resorption effect.

- Intensity parameter (λ) related to the activation frequency, hence to the number of $BMUs$ originated at each iteration.
- Length and depth parameters (a_L, b_L, a_D, b_D) to describe BMU shapes, related to life-span and number of osteoclasts.
- Proportion of pixels to be resorbed (α) related to bone imbalance, hence the life-span and number of osteoblasts.
- A percentage (κ) which allows the threshold to be calculated at each iteration and is related to the fact that the process is more or less targeted.

Running the simulation process for a given set of parameters, an initialization delay is needed before stabilization could be

reached in a context of normal bone turnover. Afterwards, modifications can be introduced to simulate biological changes over time. Figure 3 is given to illustrate the process. To compare such simulations with realistic evolutions, different scenarios can be envisaged where parameters of the process will have to be correlated to physiological observed parameters. Relevant scenarios are for example :

- For a normal bone turnover, corresponding to young healthy bone, the remodeling process is strongly targeted and the amount of bone formed equals the amount which was first resorbed. Such a normal process can be simulated using $\alpha = 100\%$ and a threshold corresponding to a percentile related to a high percentage κ.

- Estrogen deficiency after menopause is known to increase the remodeling rate. A negative imbalance, with a net excess of resorption probably due to a prolonged life-span for osteoclasts and a reduced life-span for osteoblasts, is also observed.

- Failure of the targeting process may occur when the number of viable osteocytes decreases due to a system altered by age or a disease, osteoporosis for example (see for example figure 4).

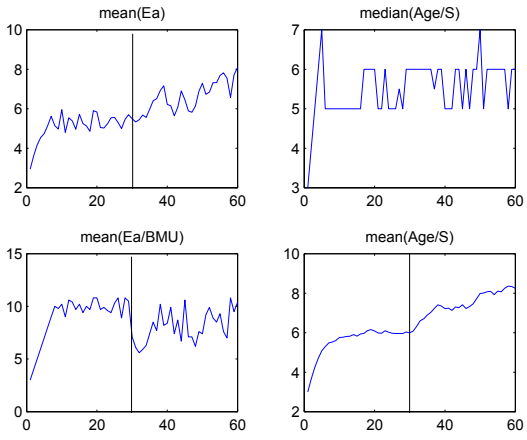


Fig. 4. A simulation without resorption $\alpha = 100\%$, strongly targeted until the 30^{th} iteration $\kappa = 85\%$, then with $\kappa = 35\%$.

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